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LETTERS AND CORRESPONDENCE

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Normal Binding of Plasma von Willebrand Factor to Platelets in Essential Thrombocythemia

To the Editor: Von Willebrand factor (vWF) is a large adhesive glycoprotein that mediates the adhesion of platelets at sites of vascular damage and also functions as a stabilizing carrier protein of coagulation factor VIII. In a recent issue of this Journal, Chow et al. [1] showed that in thrombotic thrombocytopenic purpura (TTP) binding of plasma vWF to platelets is increased, leading to intravascular platelet clumping. Microvascular thrombotic complications such as erythromelalgia, which frequently complicate the clinical course of the myeloproliferative disorder essential thrombocythemia (ET), appear to share similarities with thrombosis in TTP at first sight. As in TTP, erythromelalgia is thought to be caused by the intravascular activation and aggregation of platelets leading to occlusive thrombosis of the arterial microvasculature [2]. Immunohistochemical studies of erythromelalgic thrombi revealed abundance of vWF with little or no fibrinogen or fibrin [3], as in TTP thrombi [1]. In addition, patients with TTP may suffer from erythromelalgic symptoms responding to treatment with aspirin [4]. In addition, at platelet counts > 1000×10^9/l a deficiency of large vWF multimers in plasma is acquired [5], suggesting also an abnormal vWF-platelet interaction in ET.

We therefore evaluated vWF binding to single platelets with a flow cytometer in 12 ET patients. Four patients with an increased platelet count secondary to inflammation or splenectomy (reactive thrombocytosis, RT) and 19 normal individuals served as controls. Platelet-bound vWF in PRP adjusted to a platelet count of 200×10^9/l was directly detected with a FITC-labeled anti-vWF antibody (Dako, Glostrup, Denmark) and expressed as mean fluorescence after correction for aspecific binding. Platelets were distinguished from erythrocytes, leukocytes, and small particulate debris on the basis of characteristic platelet forward and side scatter profiles.

The patient characteristics and results of the vWF binding studies are summarized in Table I. There were no significant differences between ET, RT patients and normal subjects in platelet-bound vWF in the absence of botrocetin (a snake venom which induces vWF binding to platelet GPIb). Binding experiments in the presence of a suboptimal concentration of botrocetin (0.5 U/ml) resulted in a significant increase of platelet-bound vWF in each patient group. However, no significant differences in final platelet-bound vWF were observed, suggesting comparable binding characteristics of the vWF-platelet interaction in the different groups. In addition, treatment with aspirin did not affect binding of vWF to platelets from three ET patients; two of them were studied while having thrombotic occlusions of the acra).

TABLE I. Patient Characteristics and Results

	Controls	ET patients	RT patients
Number	19	12 (3[a])	4
Age (years)	33 (21–58)	54 (22–81)	43 (23–61)
Sex (male/female)	11/8	5/7	4/0
Platelet count ($\times 10^9$/L)	243 (150–352)	719 (414–1186)	884 (633–1100)
Bound vWF (mean fluorescence)			
− B/− ASA	75 ± 1 (66–83)	76 ± 3 (71–82)	74 ± 5 (65–83)
− B/+ ASA		71 ± 2 (47–79)[a]	
+ B/− ASA	149 ± 1 (141–155)	144 ± 3 (140–150)	151 ± 2 (148–154)
+ B/+ ASA		140 ± 4 (107–155)[a]	

Data are presented as median (range) or as mean ± SE. ET, essential thrombocythemia; RT, reactive thrombocytosis; vWF, von Willebrand factor; B, botrocetin; ASA, acetylic salicylic acid; (−) absence; (+) presence. [a]Three ET patients were studied while being on and off ASA (two of them had erythromelalgia).

Based on these data, we conclude that in ET binding of plasma vWF to platelets is comparable with that of normal control subjects. Also, at times of microvascular occlusive thrombosis (erythromelalgia) no increased vWF binding to ET platelets was observed. Our data suggest that, in contrast to TTP, the interaction between plasma vWF and platelets in ET appears to be normal. The observed decrease of large vWF multimers in plasma in association with high circulating platelet counts in ET is likely to be directly caused by the increased number of circulating platelets itself given the observation that cytoreduction of the increased platelet count to normal normalizes the multimeric distribution of vWF in plasma in ET [5]. This conclusion is further corroborated by the observation that patients with RT, who have comparable increased platelet counts, also exhibit this decrease of large vWF multimers in plasma with increasing platelet counts [5]. In contrast, unusually large forms of vWF occur in plasma in patients with chronic relapsing forms of TTP due to an inhibitor of vWF-cleaving protease in nonfamilial TTP and due to a constitutional deficiency of this protease in familial TTP cases [6]. As a result, these extremely large vWF multimers may agglutinate circulating platelets at sites with high levels of intravascular shear stress leading to intravascular platelet clumping. These extremely large vWF forms have never been observed in ET, even not in cases with documented endothelial cell damage [3]. These data indicate

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that platelet clumping in ET conceivably follows a different pathogenetic pathway than platelet clumping in TTP.

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Multifocal T-Cell Lymphoma of Bone

To the Editor: Primary lymphoma of bone (PLB) is an uncommon form of extranodal non-Hodgkin's lymphoma, most cases being of B cell origin and presenting in a single site. We report on a very unusual case of T-cell lymphoma presenting with multiple sites of bony involvement and no other evidence of nodal or extranodal involvement.

A 50-year-old male, a heavy smoker, presented with left rib and hip pain. On physical examination he had a temperature of 38.5°C and tenderness over the thoracic spine at the level of D6-7 and over the left seventh rib.

A thorough work-up was unremarkable except for a leukocyte count of 13,800/μl, and an erythrocyte sedimentation rate of 105 mm/hour. A bone scan showed multifocal increased uptake in the skull, at D7, at the seventh left rib, sternum, and the pubis which was compatible with bony metastases (Figure 1).

The search for a primary tumor was initiated. A bone marrow biopsy was normal. A CT scan revealed a soft tissue mass penetrating into the spinal canal through the left foramina at the level of D7.

An open biopsy of the left seventh rib following unsuccessful repeated CT-guided biopsies, led to the diagnosis of T-cell lymphoma, clear cell type.

Combination chemotherapy with cyclophosphamide, doxorubicin, oncovin, and prednisone (CHOP) was commenced. The pain and fever improved, but following three courses of CHOP a repeat CT scan of the dorsal vertebrae showed progression of bony destruction at the level of D7 with spreading of the soft tissue mass into the paravertebral space, and compressing the spinal cord.

The patient was treated with local irradiation (4000 rad) to D7 and subsequently underwent peripheral blood stem cell transplantation from his HLA-matched sister. He died of interstitial lung disease three months post transplantation.

Multifocal PLB is defined as a lymphoma involving two or more osseous sites without any other evidence of disease for six months. Most PLB, which constitute 5% of all extranodal lymphomas [1] present at a single site. When immunophenotype was performed most of the PLB were found to be of the B-cell type while T-cell types were extremely rare, e.g. one out

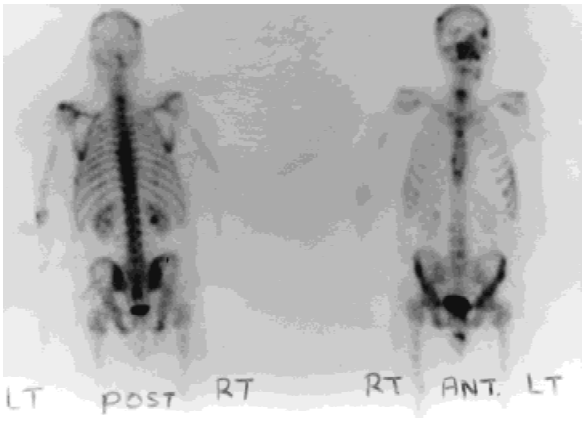

Fig. 1. Patient's bone scan demonstrating multiple hot spots of bone involvement.

of 261 patients in Ostrowski's series [2]. In Japan, where T-cell lymphoma is much more common than in the Western countries, three of 34 patients with PLB had a tumor of T-cell origin [3]. Interestingly, all four cases were morphologically of the clear cell type, as in our case.

The most common clinical presentation of bone lymphoma is osseous pain, which occurred in 80 to 100% of patients in the various series. The second most common symptom was local swelling [1,2]. Neurological deficits may be the presenting feature in patients with spinal involvement [4]. The diagnosis is best made by open biopsy. Available treatment includes surgery, irradiation, and chemotherapy. Data on results of therapy and prognosis are derived from series of patients with lymphoma of bone, which were mostly of the B-cell type [2].

Our case presents a rare clinical and immunohistological presentation of a T-cell non-Hodgkin's lymphoma. More experience is needed to define the proper treatment and prognosis of this rare entity.

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Androgen-Induced Erythrocytosis: Is It Erythropoietin?

To the Editor: We recently reported on an androgen-induced erythrocytosis in a young male bodybuilder [1]. Androgens are known to stimulate red-cell synthesis and it is thought to be secondary to an increase in erythropoietin [2]. In fact, certain androgens are used in the treatment of refractory anemias and have been shown to be potent stimulators of cell synthesis [3,4]. To date, the exact mechanisms for androgens ability to increase cell synthesis is unclear. Therefore, we decided to examine hemoglobin, hematocrit, erythropoietin and testosterone levels in nine male competitive

TABLE I. Testosterone, Erythropoietin, Hgb and Hct in Nine Bodybuilders

Subject	Test ng/ml	Epo mμ/ml	Hgb g/dl	Hct %
1	16.0[a]	7.8	17.8[a]	58.4[a]
2	15.6[a]	3.3	17.9[a]	54.0[a]
3	14.2[a]	4.2	17.5[a]	52.6[a]
4	14.9[a]	7.8	18.6[a]	57.1[a]
5	13.7[a]	4.1	18.2[a]	57.2[a]
6	17.6[a]	6.2	17.2[a]	56.1[a]
7	12.9[a]	5.0	16.1	49.4
8	15.9[a]	6.1	14.7	46.3
9	16.6[a]	5.5	16.1	47.9

[a]Elevated beyond normal range.

body builders to assess the possible relationship between testosterone, erythropoietin and erythrocytosis. All subjects have been competitive body builders for over eight years and were national level competitors or professional bodybuilders. Each subject had volunteered to participate in ongoing anabolic steroid studies at the University of North Texas Health Science Center and was provided informed consent as approved by the institutional review board. Each subject admitted to the illicit use of anabolic steroids and listed all medications taken at the time of blood collection. Testosterone and erythropoietin levels were determined by radioimmunoassay in duplicate [5]. All subjects were found to have elevated testosterone levels (normal range 3–9 ng/ml), and six subjects (67%) had elevated hematocrit levels. Suprisingly, no subjects were found to have elevated erythropoietin levels (normal range 5–26 mμ/ml). In fact, the majority of subjects were at the low end of normal range and three subjects were below the normal range, indicating a possible feedback inhibition secondary to a direct androgen-induction of erythrocyte synthesis within bone marrow (Table I). Earlier studies documenting the benefits of androgens in aplastic anemia stated that the androgens were effective despite markedly elevated erythropoietin levels prior to androgen therapy [6,7], further indicating a possible direct effect that was overlooked.

It is also quite plausible to suggest a stress-induced or spurious polycythemia in these subjects. Intense weight-lifting is highly anaerobic and coupled with extreme intermittent hypertensive episodes, may induce a polycythemia [1,8].

Interestingly, analysis of the anabolic steroids used by these subjects demonstrated that certain steroids may be more erythropoietic. All subjects found to have elevated hematocrits were using intramuscular injections of testosterone enanthate. It is possible that this form of testosterone has the molecular structure necessary to induce red-cell synthesis at the androgen receptor, or its ability to undergo enzymatic conversion to dihydrotestosterone, a more potent androgen, allows erythrocytosis to be induced.

Thus, we again found androgen-induced erythrocytosis in 67% of the body builders examined; however, no subjects were found to have elevated erythropoietin levels. It appears that certain androgens may be better at inducing red-cell synthesis through mechanisms that remain unclear. Based on these results, it is our general opinion that androgen-induced erythrocytosis may occur secondary to other mechanisms yet to be explained. The androgen-induction of erythropoietin has been established with certain androgens [2]. This small study demonstrated that the possibility of a direct androgen-induction within the bone marrow is not without merit. Future studies should focus on the elucidation of steroid-response elements within bone marrow.

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Thiamine Deficiency in a Patient Receiving Chemotherapy for Acute Myeloblastic Leukemia

To the Editor: The increasing use of highly toxic chemotherapy regimens in the treatment of cancer patients and especially hematological malignancies has lead to a parallel augmentation of patients inadequately nourished or requiring total parenteral nutrition (TPN). Thiamine (vitamin B1) has an essential role as coenzyme in carbohydrate metabolism. Clinical presentations of thiamine deficiency include Wernicke's encephalopathy characterised by blurred consciousness, ataxia, and ocular abnormalities, cardiovascular instability (or shoshin beriberi), and lactic acidosis [1,2]. The best diagnostic criterion of this rare syndrome is rapid improvement of the patient's clinical status within hours after intravenous injection of vitamin B1, although plasma thiamine level may be dosed to reinforce diagnosis. Wernicke's encephalopathy or thiamine deficiency in general are well-known complications in patients with alcoholism, malnutrition, and TPN. Thiamine deficiency has rarely been reported in malnourished cancer patients, where it may be due to decreased natural intake with other nutrients, the absence of thiamine in TPN, or both. In hematological malignancies, a few cases occurring after chemotherapy mainly in children [3–5] and allogeneic bone-marrow transplantation have been reported [6].

We report the case of a 60-year-old female with acute myeloblastic leukemia (M4-FAB) who developed a syndrome of thiamine deficiency after a second (consolidation) chemotherapy course with mitoxantrone and intermediate dose cytarabine (500 mg/m^2/12 h during 6 days). She had experienced intractable nausea and vomiting since the start of her first (induction) chemotherapy course with mitoxantrone, conventional dose cytarabine, and VP16, despite all medications. She did not receive parenteral alimentation during hospitalization for this induction therapy. There was no food intake during the 10 days spent at home after discharge from the hospital before the second chemotherapy course, during which the patient experienced the same gastrointestinal intolerance. She received 15 days of parenteral alimentation support without vitamin supply. Beginning 42 days after the onset of her consolidation chemotherapy, she presented a confusional state associated with ataxia and vertical nystagmus. The next day, she abruptly developed signs of peripheral vascular collapsus with discoloured and cold extremities despite normal arterial blood pressure. Arterial blood gases showed pH: 7.36, pCO_2: 17 mmHg, pO_2: 137 mmHg, HCO_3: 14 mEq/l, and SaO_2: 99.7%; blood chemistry revealed lactic acidemia with a lactic acid level of 10.1 (N: 0.5–2.2) mmol/l. Electroencephalographic findings were in favor of an encephalopathy. Magnetic resonance

imaging of the brain was normal. Cerebrospinal fluid examination revealed no cellular elements and its glucose, chlorine, and protein levels were normal. Because there was no other obvious cause to explain this clinical situation, 250 mg of vitamin B1 was injected intravenously with the hypothesis of thiamine deficiency in this malnourished patient. Dramatic clinical improvement was seen in a few hours: cardiovascular and metabolic components of the syndrome disappeared; the patient became rapidly more awaken and alert, but return to complete consciousness was obtained only after 2 weeks of thiamine therapy. Vertical nystagmus and gait disturbances were still present but slowly improving 7 weeks after diagnosis. The period of severe bone-marrow aplasia was of unusually long duration PN $<500/mm^3$ for 44 days, thrombocytopenia $<30000/mm^3$ for more than 70 days) after the consolidation chemotherapy.

In leukemic patients treated with highly toxic regimens, several causes may explain encephalopathy including direct neurotoxicity of chemotherapy (e.g., high-dose cytarabine), infection, intracranial bleeding, hypoxia, overdose of opioids, or benzodiazepines and various metabolic disorders (including hypo- or hyperglycemia, renal failure, hepatic failure, and primary lactic acidosis), among which Wernicke's encephalopathy should be considered. Our case underlines the importance of an efficient TPN containing sufficient amounts of vitamin B1 in the treatment of leukemic patients.

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Iron Deficiency Anemia of Unknown Etiology and/or Resistance to the Treatment: The Sole Manifestation of Adult Celiac Disease (CD)

To the Editor: Celiac disease (CD) comes to attention mostly in the search of symptoms such as chronic diarrhea, abdominal distension, and weight loss [1]. Beside this classical gastrointestinal form, it is now known that there are other clinical expression of CD characterized by minor, transient, or apparently unrelated symptoms—the secondary effects of CD [1–3]. Patients with the last group of symptoms have the typical mucosal change but it remains silent until adulthood and is detected by evaluation of these secondary effects [4–6]. Knowledge of this form with the advance in the diagnosis of disease by noninvasive screening tests, revealed that the prevalence of CD is not rare [7].

TABLE I. Laboratory Characteristics of Seven Patients

Variable	Value (median, range)
Hemoglobin (gr/dl)	9.8 (6.6–12)
MCV (fl)	70 (62–77)
Ferritin (μg/l)	5.5 (4.6–10.1)
Fe	35 (15–55)
Serum TIBC	405 (350–470)

To estimate the incidence of CD that presented as isolated iron deficiency anemia (IDA). 111 patients with IDA (male:female 13:84, median age 35, range 14–80), were enrolled in the study. IDA was diagnosed by the serum ferritin concentration, and also by blood hemoglobin concentration (Hb), erythrocyte indices, serum iron (Fe), and total iron binding capacity (TIBC). The contributing factors to IDA were determined based on age and sex. All patients received iron compounds orally as plain ferrous salts (100 mg/day). Patients were considered to be resistant to the treatment if their blood-hemoglobin-concentration deficit could not be corrected within 8 weeks and evaluated for the causes of treatment failure. A group of patients that had no obvious contributing factor for IDA and was reliable about taking the prescribed pill was re-evaluated to detect monoclonal antibodies against gliadin. Twenty-four of 111 patients failed to respond to the treatment, and 7 of them had (6.3%) pathological levels of antigliadin antibodies. They did not have symptoms related with the gastrointestinal form of CD. Serum levels of urea, electrolytes, calcium, and magnesium were normal in all these patients. The results of laboratory tests are shown in Table I. Intestinal histology was investigated in four of them and was consistent with the diagnosis of CD, except in one case. All seven patients were put on a gluten-free diet with continuing of oral iron treatment. An increase in serum iron was observed at a median of 35 days (range 30–47 days) in all patients, and resolution of the anemia occurred in a median of 67 days (range 63–71 days), which was accepted as the confirmation of CD. Intestinal biopsy, repeated after 3 months of gluten withdrawal, returned to normal.

In this study, we investigated the incidence of CD in patients with isolated IDA with unknown etiology and found that it was 6.3%. Our results were consistent with the previously reported studies, which screened CD also by its secondary effect as IDA [5–7].

It has long been known that the clinical presentation of CD has greatly changed. The serological tests identified a group of patients with atypical and also asymptomatic forms of CD. Studies demonstrated also that CD may be silent until adulthood [6]. Thus, the prevalence of CD could be more definitely estimated by the specific and sensitive serologic tests, and more patients could be put on a gluten-free diet to protect against the complications of CD. We think that in patients with IDA of unknown etiology and/or resistance to treatment, the clinician should be alert to the possibility of CD, and that screening by serological tests could provide the diagnosis.

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Remission of Pure-Red-Cell Aplasia Associated With Operative Cure of Lung Cancer

To the Editor: Pure red aplasia (PRCA) is well known to be associated with thymoma. Although the mechanistic relationship of PRCA and nonthymic malignancies remains speculative, only six cases of PRCA associated with lung cancer have been reported so far. We describe here a patient with PRCA associated with lung cancer (adenocarcinoma), who achieved hematological remission after a curative operation for lung cancer.

A 68-year-old man was admitted to Tokyo Medical University Hospital on October 1, 1997 for examination of an abnormal shadow on chest x-ray and for evaluation of anemia. The chest x-ray revealed a tumor shadow (2-cm diameter) on the upper right lung field. The laboratory data were as follows; red-blood-cell count 1.2×10^{12}/l, hemoglobin 40 g/l, hematocrit 11.6%, mean corpuscle volum 103.7, mean corpuscle hemoglobin 35.7, and reticulocytes 0%. White-blood-cell count was 9.8×10^{9}/l with normal differential and platelet count was 2.64×10^{11}/l. Biochemical findings, including renal function, were all within the normal ranges, except for increased serum iron (226 micrograms/ml, normal range 64–140). The erythropoietin level was 2160 mU/ml (normal range 8–36). Bone marrow examination revealed normo-cellular bone marrow with deficiency of erythroid series and no dysplastic changes in myeloid cells or megakaryocytes. Findings of the hematologic examination were compatible with a diagnosis of PRCA. Bronchoscopy and transbronchial lung biopsy of the right upper lung revealed adenocarcinoma. Thus, the patient was diagnosed as having primary adenocarcinoma of the lung associated with PRCA. He underwent a curative operation for lung cancer on October 28, 1997, after blood transfusion to improve the associated severe anemia (Fig. 1). Two months after the operation, the patient achieved remission of PRCA with an increasing number of erythroid cells in bone marrow.

The occurrence of PRCA in the course of nonthymic tumors is a rare event [1–5]. One plausible explanation for the association might involve impairment of immunological surveillance, because PRCA is an immunological disorder. However, the course of PRCA seems to be independent of underlying malignancies, because treatment for the associated malignancies does not lead to remission of PRCA so far. The present case suggests that the pathogenetic mechanism of PRCA might be related to associated malignancies. Therefore, we should keep in mind that some rare cases of PRCA may be associated with nonthymic tumors, and that successful treatment of the cancer may improve the hematologic condition.

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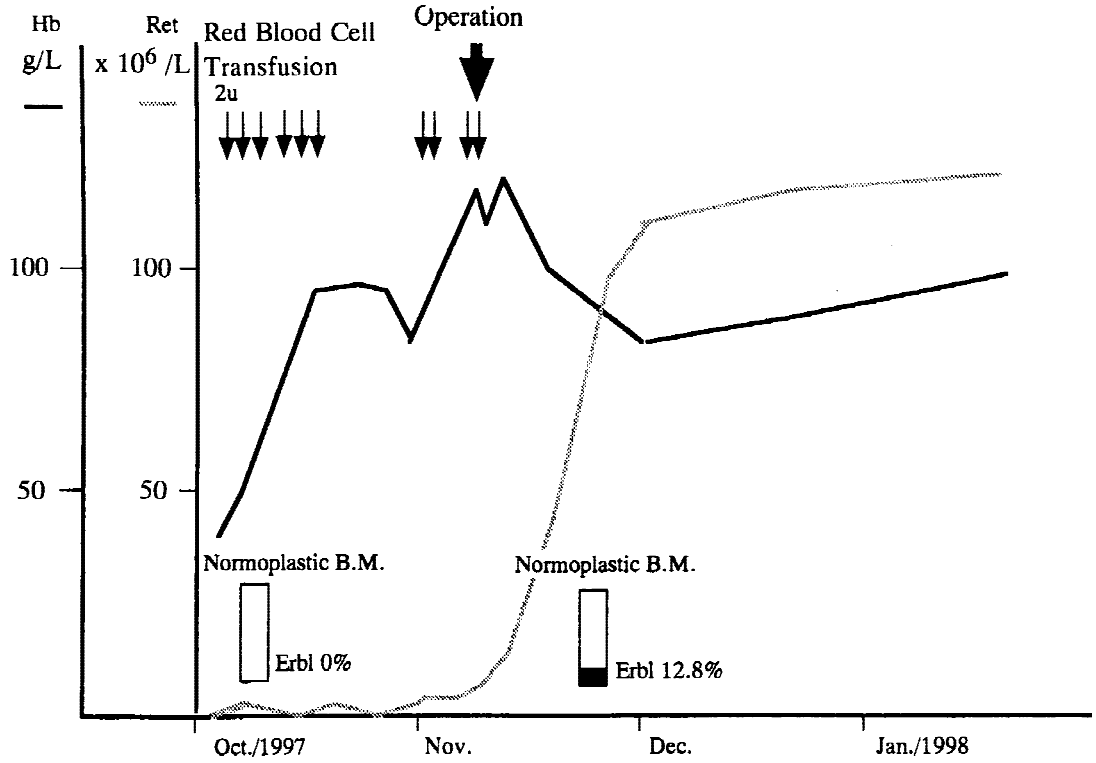

Fig. 1. Clinical and hematologic course of a patient with pure-red-cell aplasia associated with lung cancer.

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